

Correlating Functional and Structural Connectivity of Default Mode Network with Dosage of Two Candidate Vulnerability Genes of Schizophrenia

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Introduction

Schizophrenia is a complex psychiatric disorder which may be caused by multiple genetic and environmental factors. Several candidate vulnerability genes such as neuregulin 1 (NRG1) and disrupted in schizophrenia 1 (DISC1) have been identified to cause white matter and gray matter abnormalities in schizophrenia [1]. Recent advance in functional MRI (fMRI) and diffusion MRI allows us to evaluate, respectively, functional connectivity (FC) and structural connectivity (SC) in human brain [2-3], and the connectivity may be influenced by genetic factors [4]. Using resting-state fMRI, investigators have found alteration of FC in the default mode network (DMN) in patients with schizophrenia [5]. Using diffusion MRI, alteration of SC has also been reported [6]. Further, individuals with genetic risk factors for schizophrenia have been reported to have abnormal FC in DMN [7]. Taken together, FC and SC of DMN might be potential endophenotypes of schizophrenia. In this study, we combined resting-state fMRI and diffusion spectrum imaging (DSI) to examine the FC and SC of the DMN in schizophrenia, and investigated the association of connectivity with the candidate vulnerability genes.

Materials and Methods

Eleven right-handed schizophrenic patients were recruited in the study (seven males; age = 34.55 ± 7.26 years; mean positive and negative syndrome scale (PANSS) score = 56.10 ± 13.57, mean duration of illness = 6.91 ± 3.36 years). **MRI Data acquisition:** All images were acquired on a 3T MRI system with a 32-channel head array (TIM Trio, Siemens, Erlangen, Germany). DSI experiment was performed with a pulsed-gradient spin-echo diffusion EPI (TR/TE=9100/142 ms, isotropic resolution=2.5 mm, bmax=4000 s/mm², 102 diffusion gradient vectors). Resting-state fMRI was performed gradient echo EPI (TR/TE=2000/24 ms, matrix size = 64 x 64, FOV = 256mm, slice thickness = 3mm). MRI Data analysis: General linear model was applied on whole brain low-passed data to reconstruct the activation map of resting-state fMRI. The averaged time series of posterior cingulate cortex and precuneus were used as a paradigm. Six regions within DMN were obtained from the activation maps of individual subjects by one sample t-test, including bilateral posterior cingulate gyrus/precuneus (PCCL and PCCR), bilateral medial frontal lobe (MFL and MFR), and bilateral inferior parietal lobe (IPL and IPR). Fifteen nodal pairs in the DMN were determined from those six regions and the FC was derived by calculating the correlation coefficient of time series for each pair. DSI analysis was performed based on the Fourier relationship between the echo signal S(q) and the diffusion probability density function P(r) [8]. The orientation distribution function was determined by computing the second moment of P(r) along each radial direction. Tractography was reconstructed using a streamline-based algorithm adapted for DSI data using in-house software (DSI studio, <http://dsi-studio.labsolver.org/>). The regions-of-interest obtained from resting-state fMRI were used to select the connecting white matter tracts. Mean generalized fractional anisotropy along each tract was calculated to represent the SC for each pair. **Genetic data:** DNA was extracted from whole blood using a modified salting-out method [9]. The detailed genotyping methods were listed in Liu's paper [10]. The novel single nucleotide polymorphisms (SNPs) from two candidate vulnerability genes were studied, namely DISC1-2, DISC1-27, and NRG1-P3. The gene dosage was defined by how many risk SNPs a subject was carried. Gene dosage equals 1 means no risk SNPs, 6 means carried all the risk SNPs. **Statistics:** The Spearman's correlation coefficients were calculated for the following three cases, (1) gene dosage vs. FC, (2) gene dosage vs. SC and (3) gene dosage vs. PANSS.

Results

As shown in Fig. 1, significant correlations were found between the gene dosage and FC of MFR-IPL pair ($\rho = -0.700$, $p = 0.016$) and IPR-PCCR pair ($\rho = 0.628$, $p = 0.039$). Moreover, a negative correlation was found between the gene dosage and SC of PCCL-PCCR pair ($\rho = -0.632$, $p = 0.037$, Fig. 2). No significant correlation was found between the gene dosage and PANSS.

Discussion and Conclusion

With the combined resting-state fMRI and DSI, the relationships between FC, SC of the DMN and the gene dosage have been investigated in patients with schizophrenia. Significant correlations were found between the gene dosage and FCs in two pairs of DMN, namely the MFR-IPL pair and IPR-PCCR pair. Further, a significant correlation was found between the gene dosage and SC of PCCL-PCCR pair. Our results suggest that the gene dosage might influence FC and SC of the DMN. However, no significant correlation between the gene dosage and PANSS suggests that the amount of genetic factors may not directly reflect clinical symptoms. The significant correlations between the gene dosage and FC and SC of the DMN revealed in this study imply that these connectivity indices might be potential endophenotypes of schizophrenia. Further studies with larger sample size are needed to clarify the effects of individual candidate vulnerability genes on brain connectivity of schizophrenia.

References

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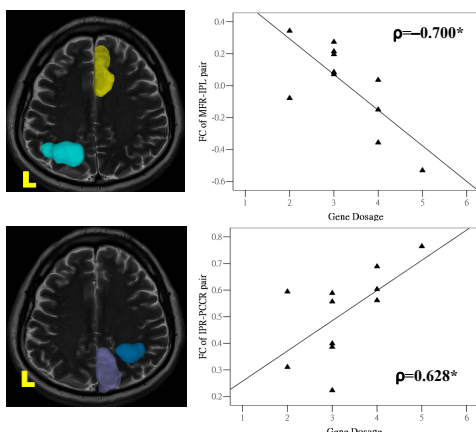


Figure 1 Significant correlations between gene dosage and FCs of two connection pairs. The connection pairs are shown with background T2 weighted images in the left panel. The functional areas are illustrated in different colors, IPL (blue), IPR (dark blue), MFR (yellow) and PCCR (purple). The scatter plots of gene dosage (x-axis) and FC (y-axis) are shown in the right panel.

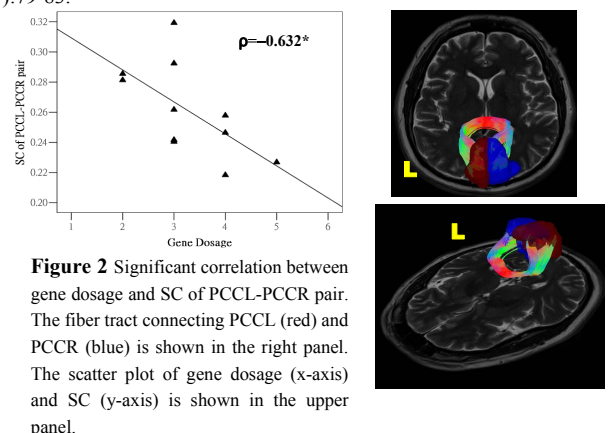


Figure 2 Significant correlation between gene dosage and SC of PCCL-PCCR pair. The fiber tract connecting PCCL (red) and PCCR (blue) is shown in the right panel. The scatter plot of gene dosage (x-axis) and SC (y-axis) is shown in the upper panel.